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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/862,855	05/21/2001	Hong Cai	S-94,652	8369

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UNIVERSITY OF CALIFORNIA
LOS ALAMOS NATIONAL LABORATORY
P.O. BOX 1663, MS A187
LOS ALAMOS, NM 87545

EXAMINER	
STRZELECKA, TERESA E	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 05/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/862,855	CAI ET AL.	
	Examiner	Art Unit	
	Teresa E. Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *5,17 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-16,18,19 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/23/01;2/4/02;9/30/02*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of species B, C, H and N in the reply filed on February 24, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 5, 17 and 20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on February 25, 2006.

3. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

4. In the reply Applicants submitted a current listing of claims, which are identical to the originally filed claims. However, in a preliminary amendment filed November 13, 2002, Applicants amended claims 1 and 8. A telephone call was made to Kenneth Sharpless on May 5, 2006 to resolve this issue, but no response was received. Therefore claims 1 and 8 will be considered in the form amended on November 13, 2002.

Information Disclosure Statement

5. The information disclosure statements (IDS) submitted on July 23, 2001 and September 30, 2002 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

6. The information disclosure statement (IDS) submitted on February 4, 2002 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. However, the references will not be printed as they are duplicates of references filed in the July 23, 2001 IDS.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. Claims 2, 8-16, 18 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Chehab et al. (PNAS USA, vol. 86, pp. 9178-9182, 1989).

Regarding claim 2, Chehab et al. teach a method of rapid haplotyping, the method comprising:

labeling at least two target sites on a segment of DNA or RNA with separate distinguishable luminescent hybridization probes, where the targets are selected genetic markers (Chehab et al. teach differential labeling oligonucleotide primers specific for target sites on the β-globin gene, the target sites being a 4-bp deletion at codons 41/42 and a C to T substitution at IVS1 and annealing the primers to genomic DNA, therefore labeling the two sites with distinguishable hybridization probes (page 9178, last two paragraphs; page 9179, paragraphs 1-3).);

forming a dilute solution containing the labeled DNA or RNA segments (Chehab et al. teach forming dilute solutions of amplified labeled fragments (page 9179, second paragraph).);

illuminating each labeled DNA or RNA segment with light beams (Chehab et al. teach illuminating the tubes with amplification reactions using light beams (page 9179, second and third paragraph).); and

detecting the presence or absence of each luminescent hybridization probe on each DNA segment to determine the haplotype of each DNA or RNA segment (Chehab et al. teach detection of the presence of hybridization probes and determination of the haplotype of each segment (page 9179, paragraphs 3-5; page 9181, second paragraph; Table 1).).

Regarding claim 8, Chehab et al. teach single nucleotide polymorphism and multibase deletion (page 9178, fifth paragraph).

Regarding claims 9 and 12, Chehab et al. teach the primers having distinguishable colors (=luminescence emission spectral distribution) (page 9178, last paragraph; page 9179, first paragraph).

Regarding claims 10 and 13, Chehab et al. teach single dye molecules (page 9178, last paragraph; page 9179, first paragraph).

Regarding claims 11, 14, 16 and 19, Chehab et al. teach DNA probes (page 9178, last paragraph).

Regarding claims 15 and 18, Chehab et al. teach single probes specific for each target (page 9179, third paragraph).

9. Claims 1-4, 8-16, 18 and 19 are rejected under 35 U.S.C. 102(e) as being anticipated by Landers (U.S. Patent No. 6,844,154 B2).

Regarding claims 1 and 2, Landers teaches a method for characterizing a genetic profile of a chromosome pair (Abstract), the method comprising:

forming multiple luminescent hybridization probes to hybridize to a wild-type and a mutant polymorphism at a first polymorphic target site and to a wild-type and a mutant polymorphism at a second polymorphic target site, where the probes for the wild-type polymorphic sites have at least one recognizable luminescent characteristic and the probes for the mutant polymorphic sites have at least a second recognizable luminescent characteristic and where the first and second polymorphic sites are located on the selected chromosome and are linked to a selected genetic characteristic (Landers teaches forming at least two luminescent pairs of probes for at least two polymorphic sites, where each pair contains a probe hybridizing to a wild-type polymorphism and a probe hybridizing to a mutant polymorphism, and where each probe is labeled with a different fluorescent label (Fig. 4; col. 3, lines 66, 67; col. 4, lines 1-12; col. 14, lines 9-21; col. 15, lines 62-67; col. 16, lines 1-29).);

forming single stranded DNA at least along segments of DNA forming the chromosome, where the single stranded DNA segments contain the first and second polymorphic sites (Landers teaches forming single stranded DNAs along fragments of genomic DNA containing the polymorphic sites (Fig. 4; col. 4, lines 13-29; col. 10, lines 50-65; col. 12, lines 16-33). Since the hybridization reaction requires denaturation of double-stranded DNA to form single strands, Landers inherently teaches formation of single-stranded DNA). Landers also teaches obtaining single-stranded DNA fragments from genomic DNA by asymmetric PCR (col. 30, lines 50-63).);

forming probe pairs from the luminescent probes, where each probe pair contains a probe specific to the first polymorphic site and a probe specific to the second polymorphic site (Landers teaches forming at least two luminescent pairs of probes for at least two polymorphic sites, where

each pair contains a probe hybridizing to a wild-type polymorphism and a probe hybridizing to a mutant polymorphism, and where each probe is labeled with a different fluorescent label (Fig. 4; col. 3, lines 66, 67; col. 4, lines 1-12; col. 14, lines 9-21; col. 15, lines 62-67; col. 16, lines 1-29).);

specifically hybridizing each probe pair in separate solutions of the single stranded DNA and determining the presence or absence of each luminescent hybridization probe in each segment of DNA in each solution to obtain a set of outputs (Landers teaches specifically hybridizing each probe pair in separate solutions of the DNA and determining the presence or absence of each hybridization probe (col. 3, lines 66, 67; col. 4, lines 1-32; col. 15, lines 62-67; col. 16, lines 1-67; col. 17, lines 1-27; col. 18, lines 13-27).); and

analyzing the set of outputs from the hybridized probes to determine the complete haplotype that characterizes the genetic profile of the selected chromosome pair (Landers teaches analyzing the set of outputs to determine the haplotype of the chromosome pair (col. 16, lines 62-67; col. 17, lines 1-28; col. 20, lines 65-67; col. 21, lines 1-30).).

Regarding claim 2, Landers teaches separating the hybridized DNA molecules into separate container and analysis of the molecules by flow cytometry, therefore they inherently teach diluting the labeled molecules (col. 3, lines 66, 67; col. 4, lines 1-12; col. 16, lines 30-62).

Regarding claim 3, Landers teaches haplotyping whole chromosomes and organisms (col. 2, lines 21-38; col. 6, lines 5-34; col. 7, lines 41-67; col. 8, lines 1-12).

Regarding claim 4, Landers teaches detecting the fluorescence from each probe and cross-correlating the information to indicate the presence or absence of the probes on the sample (col. 16, lines 63-67; col. 17, lines 1-28).

Regarding claim 8, Landers teaches SNPs (col. 2, lines 21-38), deletions, multiplications or substitutions (col. 15, lines 18-22).

Regarding claims 9 and 12, Landers teaches distinguishable probe characteristic being its color (= luminescence emission spectral distribution) (Fig. 4; col. 16, lines 51-67; col. 17, lines 1-28).

Regarding claims 10 and 13, Landers teaches single dye molecules (col. 17, lines 29-67; col. 18, lines 1, 2).

Regarding claims 11, 14, 16 and 19, Landers teaches DNA probes (col. 5, lines 22-67).

Regarding claims 15 and 18, Landers teaches single probes (Fig. 4; col. Col. 3, lines 66, 67; col. 4, lines 1-9).

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 6, 7 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Landers (U.S. Patent No. 6,844,154 B2) and Nie et al. (Science, vol. 266, pp. 1018-1021, 1994).

A) Landers teaches detection of single fluorescent DNA molecules (col. 3, lines 66, 67; col. 4, lines 1-9) and detection of fluorescent molecules using a fluorometer, but does not teach detection with a confocal microscope.

B) Regarding claims 6 and 7, Nie et al. teach detection of single fluorescent molecules in solution using far-field confocal fluorescence microscopy and scanning probe volume (page 1018, third and fourth paragraphs; page 1019, third paragraph; Fig. 1). Nie et al. teach detection of single DNA molecules using the instrument (page 1019, third paragraph).

Regarding claim 21, Nie et al. teach detection of analyte concentrations of 10^{-11} to 10^{-9} M (page 1018, fourth paragraph; Fig. 1), anticipating the range of between 100 nM to sub-fM.

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to have used confocal microscope detection of single fluorescent molecules of Nie et al. in the method of haplotyping of Landers. The motivation to do so, provided by Nie et al., would have been, as stated by Nie et al.:

"Through the use of a high-efficiency photon detection system, we examine in detail the diffusive movement and emission characteristics of single molecule as well as the photophysical behavior of a single-chromophore molecule in solution. We also report the first detection of individual fluorescein molecules in aqueous media and the extraordinary detection sensitivity achieved for common fluorescent dyes in various sampling environments. In a preliminary study, we have detected single DNA bases labeled with one fluorescent tag and observed in real time gyration radius changes for individual large DNA fragments (~ 2000 bp)." (page 1018, third paragraph), and

" These features are expected to allow important applications such as enhanced Raman spectroscopy at the single-molecule level and on-line fluorescence identification and sorting of individual molecules and quantum-confined nanostructures. The extraordinary sensitivity achieved in this work allows the direct, real-time study of the dynamics of a single molecule and the chemical and biochemical reactions that such a molecule may undergo in solution." (page 1021).

12. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E. Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Teresa E Strzelecka
Primary Examiner
Art Unit 1637

Teresa Strzelecka
5/13/06